

Title: Factor V Leiden Thrombophilia *GeneReview* Supplemental Information:
Thrombosis NOT Convincingly Associated with Factor V Leiden Thrombophilia

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Note: The following information was provided by the author listed above and has not been reviewed by *GeneReviews* staff.

Thrombophilia includes arterial thrombosis, myocardial infarction, stroke in fetuses, children, and adults.

Arterial thrombosis. The role of factor V Leiden in arterial disease is controversial, with conflicting results from different studies. Most studies of unselected adult populations found no association between presence of a factor V Leiden allele and an increased risk for myocardial infarction or stroke [Cushman et al 1998, Linnemann et al 2008b]. A meta-analysis of 33 studies and including 25,053 individuals found no significant association with myocardial infarction, stroke, or peripheral vascular disease either collectively or individually [Kim & Becker 2003]. However, a more recent larger meta-analysis found that a Leiden variant conferred a moderately increased risk for coronary disease and myocardial infarction [Ye et al 2006]. Although consensus holds that the Leiden variant is not a major risk factor for MI or stroke, some data suggest that it may contribute to the risk for arterial thrombotic events in selected subgroups of individuals.

Myocardial infarction. The results of several studies suggest that the Leiden variant may contribute to myocardial infarction in younger individuals and in those with concomitant cardiovascular risk factors.

- One study reported a significantly increased risk for myocardial infarction in young women with other cardiovascular risk factors, particularly smoking. Young women with heterozygous for Leiden variant who smoked had a 30-fold increased risk for myocardial infarction compared to women with neither risk factor [Rosendaal et al 1997].
- Several other studies found that the simultaneous presence of prothrombotic variants, including the Leiden variant, and one or more cardiovascular risk factors substantially increased the risk for acute myocardial infarction. The combination of a prothrombotic variant and smoking was associated with the highest risk (odds ratio range: 6-18) [Doggen et al 1998, Inbal et al 1999].
- Two studies found a significantly higher prevalence of a factor V Leiden allele in young individuals with premature myocardial infarction and normal coronary angiography than in matched controls with significant coronary artery disease, with odds ratios of 2.6 and 4.7, respectively [Mansourati et al 2000, Van de Water et al 2000].
- A case-control study found that a heterozygous Leiden variant was associated with a significant two- to threefold increased risk for myocardial infarction. All of the individuals with a Leiden variant and myocardial infarction had coexisting cardiovascular risk factors [Middendorf et al 2004].

- The risk for arterial thrombosis in Leiden variant homozygotes is unknown, as very few homozygous individuals were included in the available studies.

Stroke in adults. Most studies of unselected adult populations did not find a significant association between factor V Leiden and ischemic stroke [Cushman et al 1998, Lalouschek et al 2005]. There was no difference in the prevalence of factor V Leiden between unselected individuals with severe carotid atherosclerosis and healthy controls, even in the subgroup with symptomatic disease [Marcucci et al 2005]. Although the available data suggest that factor V Leiden is not a general risk factor for stroke, it may contribute in selected populations.

A factor V Leiden allele was associated with a threefold increased risk for stroke in individuals younger than age 45-50 years; the risk was even higher in women in this age group (odds ratio range: 4-6) [Margaglione et al 1999, Aznar et al 2004].

The interaction of factor V Leiden with other vascular risk factors may increase the risk for ischemic stroke.

- Two studies found that young women with a factor V Leiden allele who used oral contraceptives had a nine- to 13-fold increased risk for stroke, compared to women with neither risk factor [Slooter et al 2005, Martinelli et al 2006].
- Several studies also found a six- to ninefold increased risk for stroke in young adults and women up to age 60 years [Margaglione et al 1999, Lalouschek et al 2005, Slooter et al 2005]. Women with factor V Leiden who smoked had a nearly ninefold higher risk for stroke than women without either risk factor [Lalouschek et al 2005].
- The combination of a factor V Leiden allele with one or more other cardiovascular risk factors (hypertension, diabetes, hypercholesterolemia) was associated with a nearly 11-fold increase in stroke risk [Margaglione et al 1999].

Arterial thromboembolism may also occur "paradoxically" through a patent foramen ovale (PFO) in the heart of individuals with venous thrombosis [Karttunen et al 2003]. In a recent meta-analysis, individuals with a factor V Leiden mutation or the prothrombin gene mutation had a twofold increased risk for PFO-related stroke [Pezzini et al 2009].

Stroke in children. Arterial ischemic stroke in children usually occurs in the setting of multiple predisposing factors [Barnes & Deveber 2006]. Data on the association of thrombophilia with ischemic stroke are conflicting [Mackay & Monagle 2008]. Studies that support an association between a factor V Leiden mutation and stroke in children:

- The majority of published case-control studies found a significantly increased prevalence of a factor V Leiden mutation in children with ischemic stroke (17%-23%) compared to control children (3%-4%), with odds ratios of 4 to 5 [Zenz et al 1998, Nowak-Göttl et al 1999, Kenet et al 2000, Duran et al 2005].
- Analysis of the data from five studies suggests that the mutation confers an overall fourfold increase in stroke risk [Barnes & Deveber 2006].

Studies that do not support an association between a factor V Leiden mutation and stroke in children:

- A meta-analysis reported that children with a factor V Leiden allele had a statistically insignificant lower risk for a first ischemic stroke (odds ratio 1.2) [Haywood et al 2005].
- Heterozygosity for a factor V Leiden mutation was not significantly associated with arterial or venous stroke in newborns [Miller et al 2006].
- Several studies including older children found no significant association with recurrent stroke, although a nonsignificant trend was found in one study [Strater et al 2002, Ganesan et al 2006].

Stroke in the fetus. Arterial thrombosis may also occur in the fetus as a result of placental venous thrombi entering the fetal circulation, crossing the foramen ovale, and entering the cerebral arterial vasculature. The data on the role of factor V Leiden in perinatal ischemic stroke are conflicting.

- In one study, a neonatal or maternal factor V Leiden mutation was associated with a fourfold and eightfold increased risk for perinatal ischemic stroke, respectively [Simchen et al 2009].
- Another study of mother and infant pairs found no association [Curry et al 2007].

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